AFTER FINAL

Practitioner's Docket No.: 868_012 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI		
Serial No.:	10/587,320	Group Art Unit:	1618
Filed:	May 10, 2007	Examiner:	Nissa M. Westerberg
Conf. No.:	4731		
For:	PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY		

OK TO ENTER: /N.M.W./
09/22/2010

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR RECONSIDERATION

Sir:

In response to the Final Office Action mailed June 21, 2010, Applicants respectfully request reconsideration and withdrawal of the rejections of record based on the following arguments. Claims 10-12, 14, 18, 20 and 21 are pending herein.

Claims 10-12, 14, 18, 20 and 21 were rejected under §103(a) over Mylari in view of Crary, and over Akita in view of Crary and Wani. These rejections are respectfully traversed.

Applicants respectfully submit that the arguments presented in the paper filed June 8, 2010, as well as the arguments presented to date, establish patentability of all pending claims.

Applicants submit the following additional remarks in rebuttal to the comments appearing in the most recent Office Action.

The Examiner states that "structural similarity is not required if the art recognizes that the various compounds have the same activities" (Office Action, page 4, lines 2-4). Applicants respectfully withdraw the rebuttal about structural similarity.

The Examiner states that "the compounds of Crary are known to decrease diabetic complications" (Office Action, page 4, lines 5-6), and "Crary teaches that agents which decrease complications from diabetes, albeit at an earlier stage in the process by lowering blood glucose levels whose long term levels are reflected by the HbA1c level, prevents or treats macular edema of human diabetic retinopathy" (Office Action, page 6, lines 6-9). Applicants respectfully disagree with the Examiner's statements. The term "diabetic complications" is not found in Crary. Rather, the expression "the complications of capillary leakage and bleeding in ... " (Col. 3, line 4-5, Col. 4: lines 48-49, 54-55, 61-62) is often found in the reference. The noted term just means the two characteristic findings in ocular fundus such as leakage and bleeding from the retinal capillary, and the term is used in a limited context that defines the clinical features in diabetic retinopathy. "Diabetic complications" used as a comprehensive term including various diseases such as neuropathy, nephropathy or retinopathy, is not found in Crary; even more, the expression "decrease complications from diabetes" also is not found in Crary. As mentioned above, Applicants are unable

to accept the Examiner's assertions that, just as the compounds of Crary, aldose reductase inhibitors, which are useful for diabetic complications, would also prevent or treat macular edema of human diabetic retinopathy.

The Examiner states that "the Crary reference was cited to show that condition known in the art to be useful for the treatment of diabetic retinopathy are also useful in the treatment of diffuse macular edema in diabetic patients" (Office Action, page 4, lines 12-15), and states "Patient 4 with diffuse macular edema and background diabetic retinopathy was followed for four years and visual acuity was maintained while on the supplementation regimen" (Office Action, page 5, lines 15-17). Applicants respectfully apologize for their oversight regarding the effect in patient 4. Applicants admit that the efficacy of selenium plus vitamin E is described in Crary. However, it is not necessarily the case that a compound showing an effect on diabetic retinopathy is also useful for diffuse macular edema in diabetic patients. The record to date more than adequately proves this point.

Applicants herein provide additional evidence in support of the above position. Calcium dobesilate significantly ameliorates the level of diabetic retinopathy in diabetic patients (see enclosed Reference 1, page 1597; left column, lines 1-5). However, Haritoglou et al. (see enclosed Reference 2, page 1370; left column, lines 10-14) reports that calcium dobesilate could neither prevent the occurrence of macular edema nor reduce the development of macular edema during as long as a 5-year follow-up period, which is considered to be a sufficient duration to evaluate the effect of the drug on diabetic retinopathy. Clinically Significant Macular Edema (CSME), which is a primary endpoint used in Haritoglou, indicates the severity of macular

edema (see enclosed Reference 3, Page 762; left column, lines 8-10), and is a term commonly used for evaluating macular edema. From the above publications, it is clear that a compound that is useful for diabetic retinopathy is not always useful for macular edema.

In contrast, an effective agent for macular edema is not always useful for diabetic retinopathy. Applicants previously explained that PKC-β inhibitor reduced the progression of macular edema in diabetic patients (see enclosed Reference 4, previously-submitted, page 2221: Abstract: Conclusion), but did not prevent the progression of diabetic retinopathy (see enclosed Reference 5, previously-submitted, page 2188; Abstract, lines 1-3 from the bottom). From these references, it is difficult to state that an effective agent for macular edema is also useful for diabetic retinopathy. The evidence of various agents regarding the efficacy on retinopathy or macular edema in diabetic patients is summarized in the following Table 1:

Table 1 - Clinical study in human

Agent	**Diabetic retinopathy**	**Diabetic macular edema**
Calcium dobesilate	Effective (Ref 1)	Non-effective (Ref 2)
PKC-β inhibitor	Non-effective (Ref 5)	Effective (Ref 4)
Selenium and Vitamin E	Effective (Crary)	Effective (Crary)
SNK-860	Non-effective	Effective

This evidence clearly proves that, while some agents are useful for both retinopathy and macular edema, others are useful for only one disease. Therefore, Applicants cannot accept the conclusion drawn by the Examiner, based on only the statements in Crary.

Applicants previously submitted comparison data of SNK-860 with epalrestat in a monkey model. Epalrestat is an agent showing efficacy on diabetic retinopathy in clinical trials, but no efficacy on macular edema in diabetic monkeys. The data clarifies that in aldose reductase inhibitors, epalrestat, which shows an efficacy on diabetic retinopathy, is not useful for macular edema. Applicants respectfully submit, therefore, that the data refutes the Examiner's conclusion that "an effective agent for diabetic retinopathy is also useful for macular edema." As stated previously, Applicants have clearly rebutted the Examiner's assertion that "an effective agent for diabetic retinopathy is also useful for macular edema in diabetic patients." Therefore, the obviousness rejections based on a combination of the Crary reference and the other applied references should be withdrawn.

The Examiner states "It is unclear whether by "DME" Applicants are referring to "diffuse macular edema" or "diabetic macular edema" or are the two terms being used interchangeably" (Office Action, page 5, lines 2-4). The term "DME" used by Applicants in the Request for Reconsideration filed June 8, 2010 means diffuse macular edema. Applicants apologize for any confusion this may have caused the Examiner, and sincerely ask the Examiner to read "DME" as used in the Request for Reconsideration as "diffuse macular edema."

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, the Examiner is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

September 20, 2010
Date

Stephen P. Burr
Reg. No. 32,970

SPB/CW/tlp

Attachments:

1. Ribeiro, ML. et al. "Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomized double-blind study." Graefe's Arch Clin Exp Ophthalmol 2006; 244:1591-1600.
2. Haritoglou, C et al. "Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomized, double-blind, placebo-controlled, multicentre trial." Lancet 2009; 373:1364-1371.
3. Early treatment diabetic retinopathy study research group. "Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema." Early treatment diabetic retinopathy study. Report Number 2. Ophthalmology 1987; 94:761-774.
4. PKC-DRS2 Group et al. "Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy." Ophthalmology 2006; 113: 2221-2230.
5. The PKC-DRS Study Group. "The Effect of Ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy." Diabetes 2005; 54:2188–2197.

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